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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/410,462	10/01/1999	ANGELICA WILLIAMS	ONYX1046-ORD	6889

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EXAMINER	
ANGELL, JON E	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/410,462	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-13,15,17-20,22,23 and 26-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *26-28* is/are allowed.

6)☒ Claim(s) *6-13,15,17-20,22,23 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 11/15/2006.

Claims 6-13, 15, 17-20, 22, 23, 26-34 are currently pending and are examined herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 11/15/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6, 7, 11-13, 15, 17, 18 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by anticipated by U.S. Patent No. 6,080,578 (Bischoff et al., previously of record), for the reasons of record which are reiterated below.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Bischoff et al. teach a cytopathic adenoviral comprising a mutation in an E1A CR2 RB family member binding region as well as methods of using the vector for preferential therapy and prophylaxis of neoplasia compared to non-neoplastic cells (e.g., column 3, lines 7-29; column 4, lines 1-55; etc.) Bischoff et al. teach that the mutant adenoviral vector can comprise a mutation can be a e.g., a deletion, substitution frameshift in CR2 domain, amino acids 120-139 (see column 10, lines 10-25), and specifically teaches a mutant comprising a deletion of amino acids 2-150 (dl 1010) which completely deletes the CR1 and CR2 domains (see column 10, lines 25-40). Bischoff et al. teach that the mutant adenoviral vectors can be used to treat various different tumors in a subject by directly administering the vector to the tumor, for instance by swabbing a solution comprising the vector directly on a tumor or by direct injection (e.g., see column 16, lines 26-53). It is noted that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor, as well as non-dividing non-cancerous cells. Therefore, administering the vector taught

by Bischoff to a subject having a tumor would necessarily result in substantially and selectively killing dividing endothelial cells (including dividing microvasculature) and cancer cells in the subject.

Therefore, Bischoff et al. anticipates the instant claims.

Claim 22 is rejected under 35 U.S.C. 102(b) as being anticipated by Whyte et al. (J. Virol. 1988, previously of record), for the reasons of record which are reiterated below.

The instant claim is drawn to a pharmaceutical composition comprising an Rb binding site adenoviral mutant in physiological solution where said adenoviral mutant is dl922/947.

Whyte teaches several mutant adenoviral vectors including the dl922/947 vector (e.g., see Figure 4) and further teaches that the vectors were administered to cells in tissue culture (e.g., see page 258, column 2) thus indicating that the vectors were in a physiological solution (also see page 258, first column). Therefore, Whyte anticipates the instant claim.

Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Jelsma et al. (Virol. 1989, previously of record) for the reasons of record which are reiterated below.

The instant claim is drawn to a pharmaceutical composition comprising an Rb binding site adenoviral mutant in physiological solution where said adenoviral mutant is dl1107.

Jelsma several mutant adenoviral vectors including the dl1107 vector (e.g., see Figure 1) and further teaches that the vectors were administered to cells in tissue culture (e.g., see Table 2) thus indicating that the vectors were in a physiological solution (also see page 121, second column). Therefore, Jelsma anticipates the instant claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-13, 15, 17-20 and 29-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: methods of treatment comprising administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region directly to the target cells, does not reasonably provide enablement for the full scope of the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is a method for killing dividing endothelial cells while not killing non-dividing endothelial cells by administering a mutant cytopathic adenovirus to a subject having said cells.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The claims are broad in the sense that they encompass any route of administration, including general systemic delivery and delivery of the adenovirus at a site distal to the target cells such that the adenovirus must travel through the subjects system to reach the target cells.

The instant claims are not fully enabled because the prior art recognizes that there are major caveats for non-direct delivery of therapeutic nucleic acids (including adenoviral vectors). For instance, the art recognizes that in vivo administration of therapeutic nucleic acids is plagues by inefficient delivery to the target cells due to many factors including the host's immune response (e.g., see Dang et al. or Eck et al. previously of record).

With respect to adenoviral vectors, Green et al. (Cancer Gene Therapy, 2002; 9:1036-1042) teaches:

> "The development of a targeted adenoviral vector, which can be delivered systemically, is one of the major challenges facing cancer gene therapy. The virus is readily cleared from the bloodstream, can be neutralised by pre-existing antibodies, and has a permissive cellular tropism. Clinical studies using the ONYX virus have shown limited efficacy, but there are several hurdles to overcome to achieve an effective tumor-specific systemic therapy. In this review, we have summarized the various strategies used to overcome the Limitations of adenoviral-mediated gene delivery." (See abstract).

Green et al. also notes that:

> "In clinical trials using ONYX-015, the majority of patients presented with neutralizing antibodies and almost all showed a significant increase in titer after the initial virus injection. There are also significant concerns over vector immunogenicity following the death of a patient after hepatic artery infusion of a replication-defective Ad vector. It is thought that viral capsid proteins are involved in the acute cytokine release observed shortly after virus administration." (p. 1039, references omitted).

The specification provides examples which indicates that the mutant adenovirus can selectively kill dividing cells (and not quiescent cells) in vitro (Examples 1 and 2). Example 3 indicates that the mutant virus was delivered by direct injection into tumors of athymic mice and resulted in tumor regression (see Figure 4). The specification provides a working example (Example 4) which discloses intranasal inoculations of the mutant or wild type adenovirus to a immunocompetent rat and indicates that the intranasally administered mutant adenovirus divides less in the quiescent lung cells than the wild type virus. It is noted that intranasal delivery directly delivers the virus to cells from the nasal passage to the lungs. Furthermore, as previously pointed out, the claims encompass treating any tumor by any route of administration. As such, in order for the specification to be enabling for the full scope encompassed by the claims it would have to demonstrate that intranasal delivery could be used to specifically and effectively deliver the mutant adenoviral vectors to the target cells wherein the target cells are distal to the site of administration. For instance, in order to be enabling for the full scope of the claims the specification would have to provide a disclosure which enables general (e.g., systemic) delivery of the vector such that the general (systemic) delivery results in the vector specifically reaching the targeting site and substantially and selectively killing dividing edothelial cells without the concomitant killing of non-dividing endothelial cells at the target site without effecting cells at non-target sites. The specification does not provide such a disclosure.

The level of the skill in the art is deemed to be high.

Considering the breadth of the claims (any route of administration), the state of the prior art at the time filing in view of the examples and guidance provided in the specification, it is clear that additional experimentation would be required to be able to predictably practice the claimed method to the full scope encompassed by the claims. The additional experimentation would be trial and error experimentation to attempt to overcome the caveats taught in the prior art. Overcoming these obstacles would amount to an inventive step(s) over the prior art. Therefore, it is concluded that the specification does not provide an enabling disclosure for the instant claims and additional experimentation is required. The amount of additional experimentation is not routine and amounts to an undue amount of additional experimentation

Response to Arguments

Applicant's arguments filed 11/15/2006 have been fully considered but they are not persuasive.

Applicants argue that the rejection of claims under 35 U.S.C. §102(e) based on the disclosure of the Bischoff et al reference is improper because Bischoff et al does not teach all of the elements of the present invention. Specifically, Applicants contend that Bischoff et al does not teach or provide guidance which would lead one of ordinary skill in the art to a method for preferential killing of dividing endothelial cells compared to quiescent endothelial cells using a replication competent adenovirus.

In response, it is noted that claimed method comprises steps that are identical to those of a method taught by Bischoff et al.; therefore, the same result would have been achieved in the prior art method.

Applicant is reminded that MPEP § 2112.01 indicates, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.'"

Applicants assert, for the sake of argument, that in the case of a claimed method comprising steps identical to those of a method practiced in the prior art, and where the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result cannot be said to constitute anticipation (citing *In re Marshall*, 578 F.2d 301,198 USPQ 344). Applicants also assert that, in general, a limitation or the entire invention is inherent and in the public domain if it is the "natural result flowing from" the explicit disclosure of the prior art (citing *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955,970, 58 U.S.P.Q.2d 1865 (Fed. Cir. 2001). Applicants argue that Bischoff et al contains no teaching or suggestion that directing one of ordinary skill in the art to specifically use mutations in the E1A-CR2 region of the E1A RB family member binding region for substantial and selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells; and, in particular, the reference of Bischoff, et al., contains no teaching or suggestion regarding the unexpected and superior properties of mutations in the E1A-CR2 region. Applicants contend that for a claim to be inherent in the prior art it "is not sufficient that a person following the disclosure sometimes

obtain the result set forth in the [claim]; it must invariably happen", citing *Standard Oil Co. v. Montedison, S.p.A.*, (3d Cir. 1981).

In response, it is respectfully pointed out that, as indicated above, Bischoff et al. teaches a cytopathic adenoviral vector comprising a mutation in an E1A CR2 RB family member binding region, as well as methods of using the vector for treatment of tumors by directly administering the vector to the tumor. Therefore, Bischoff et al teaches administering a vector which meets all of the structural limitations of the claims directly to a tumor. In other words, Bischoff et al. teaches administering, directly to a tumor, the exact same vector that is used in independent claims 11, 12 and 15. Applicant is reminded that MPEP § 2112 indicates,

> "[T]he claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."; and, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)."

Since the vector used in the process taught by Bischoff et al. meets all of the structural limitations of the vector used in the method of the instant claims, it would, absent evidence to the contrary, necessarily have all of the same functions. Therefore, administering the vector taught by Bischoff et al directly to a tumor would, in the absence of evidence to the contrary, necessarily result in selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells that are present in the tumor. It is respectfully pointed out that MPEP § 2112.01, in addition to that which was indicated above, also indicates, "'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.' *In re Spada*, 911 F.2d 705, 709, 15

USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by **evidence** showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)." (Emphasis added). In the instant case, Applicants have not submitted **evidence** showing that the method taught in the prior art (Bischoff et al.) would not necessarily result in selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells that are present in the tumor.

Although Bischoff et al. is silent with respect to the limitations in the instant claims that the method would result in selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells, Bischoff et al. anticipates all of the claimed active method steps, so the function effects of the claimed methods are considered to be inherent in the method steps taught by Bischoff et al.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Applicants contend that the rejection of claims under 35 U.S.C. 102(b) as being anticipated by Whyte et al. and Jelsma et al. is improper because Whyte et al and Jelsma et al. only teach physiological solutions for administration to cells in culture, not pharmaceutical compositions. Applicants point to the specification on page 13, lines 7-20 as support for their argument that pharmaceutical compositions of the present invention generally contain a pharmacologically effective dosage of adenovirus and are free of particulate matter other than the desired adenoviral vector, and that the pharmaceutical compositions are suitable for administration to a patient.

In response it is respectfully pointed out that the passage on page 13 of the specification is not a limiting definition for the term "pharmaceutical composition", rather it merely exemplifies that which may be considered pharmaceutical composition. In the absence of a limiting definition, it is proper to give the term its broadest reasonable interpretation consistent with the specification. In this case, the references teach the products in physiological solutions that are administered to cultured living cells. The cultured living cells are considered an acceptable model for direct delivery to cells that are in a subject (i.e., *in vivo*). Since the physiological solution is suitable for administration to living cultured cells, the physiological solution is also considered suitable for direct administration to cells *in vivo.* Thus, the compositions taught by Whyte et al and Jelsma et al are considered to be "pharmaceutical" compositions in the absence of a clearly limiting definition.

Applicants respectfully request clarification concerning why a new rejection is being reasserted based on previously applied references wherein the previous rejections were withdrawn.

In response, the art rejections were against independent claim 21 as well as dependent claims 22-24 (e.g., see the 1/17/2002 Office Action). However, in the amendment filed 7/17/2002, Applicants cancelled independent claim 21, obviating the rejection of claim 21 and rendering dependent claims 22-24 indefinite as they dependent on a cancelled claim. Since claims 22-24 were indefinite for depending on a cancelled claim, the claims were not considered further as was impossible to determine the metes and bounds of the indefinite claims. Accordingly, the rejection was not withdrawn in the 4/20/2005 Office Action because claims 21 and 25 were cancelled and claims 22-24 were indefinite for the reasons indicated above. Upon further consideration of the art Whyte et al and Jelsma et al references in view of the claim amendment filed 4/28/2006, it was determined that Whyte et al. and Jelsma et al. anticipated the indicated claims for the reasons indicated above.

With respect to the rejection of claims under 35 USC 112, first paragraph, Applicants first request clarification of the rejection as it applies to claims 22, 23, 26-28, which are composition claims.

In response, upon further consideration, the instant claims, which are composition claims, are considered to have an enabled embodiment, that being the treatment comprising directly administering the compositions to tumors. Therefore, the rejection of claims 22, 23, 26-28 under 35 U.S.C. 112, first paragraph is withdrawn.

With respect to the rejection of claims 6-13, 15, 17-20 and 29-34 under 35 U.S.C. 112, first paragraph, it is respectfully pointed out that the only issue remaining is the route of administration. It is noted that the claims encompass administering the vector to a subject by any route of administration, including general systemic delivery, including delivery of the vector to a site distal to the target cells such that the vector must travel through the subjects system to reach the target cells. The art of record teaches that generalized (e.g., systemic) delivery of vectors is unpredictable for a number of reasons, including the host's immune response. The specification does not provide overcome the problems recognized in the art because it does not provide guidance on how to effectively deliver the vector to a specific target sight by any route of administration other than direct delivery. It is acknowledged that the specification discloses *in vitro* examples as well as *in vivo* models where (1) the vector is directly delivered into tumor cells in a nude mouse model (i.e., an immunocompromised mouse), and (2) the vector was delivered to lung tissue by intranasal administration of the vector to a rat. These examples only provide guidance which enables direct delivery of the vector to the target site, and do not provide guidance on how to overcome the problems recognized in the art with respect to non-direct (e.g., systemic) delivery. Applicant is reminded that MPEP § 2164.01 indicates that the application, when filed, must contain sufficient information to enable one of skill in the art how to make and use the claimed invention. In other words, the claims must be enabled at the time of filing. In the instant case, in view of the art of record which demonstrates that delivering a vector to specific target cells by general, non direct-delivery is unpredictable, the specification which only

provides guidance for direct delivery, the specification does not provide an disclosure which enables the full scope encompassed by the claims.

Applicants argue that a patent may be enabling even though some experimentation is necessary; and, a considerable amount of routine experimentation is permissible if the specification provides a reasonable amount of guidance.

In response, the specification does not provide a reasonable amount of guidance to enable the full scope encompassed by the claims.

Applicants submit, in view of applicant's teachings regarding the efficacy of the methods of the present invention that delivery of the virus to the target cells via intranasal delivery supports an intranasal route of administration for the methods of the present invention relating to substantial and selective killing of dividing endothelial cells compared to quiescent endothelial cells.

In response, it is acknowledged that the specification does provide an enabling disclosure for intranasal delivery of the vector to target cells that are located in the nasal passage and to the lungs, but not for intranasal delivery to target cells that are distal to the nasal passage and lungs. For instance, the specification is not enabling for intranasal administration where the target cells are cells located in the pancreas, cervix, bones, etc.

Applicants argue that the specification teaches a variety of formulations and methods of administration for the vector for use in the claimed methods and refer to the specification on pages 13-15. In addition, applicants refer to U. S. Patent No. 5,677,178 incorporated by reference in its entirety, which indicates that an adenovirus suspension may be inhaled as a mist

(e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladdercancer).

In response, it is noted that all of these administrations appear be administrations that directly deliver the vector to the target tissue.

Applicants assert that, even if, for the sake of argument, some further experimentation is necessary, so long as the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed, a considerable amount of routine experimentation is permissible. See, e.g., Ex parte Forman, 230 USPQ 546, 547 (PTO Bd.

In response, the additional experimentation required would be trial and error experimentation to attempt to overcome the caveats taught in the prior art, without a predictable outcome. Furthermore, overcoming the obstacles recognized in the art would amount to an inventive step(s) over the prior art. Accordingly the additional experimentation required is

beyond routine, and constitutes an undue amount of additional experimentation in order to enable the full scope encompassed by the claims.

Applicants take issue with the references which discuss the shortcomings of general gene therapy and gene delivery methods because the references do not address the use of oncolytic adenoviruses.

In response, it is acknowledged that the indicated references do not address the use of oncolytic adenoviruses. However, the do demonstrate there are a number of caveats with respect to generalized (e.g., non-direct) administration of nucleic acid vectors. It is noted that the oncolytic adenovirus is a nucleic acid vector, and, as such, citing these references is appropriate.

With respect to the Green et al reference, applicants note that Green et al. is a review article published after the priority date of the instant application.

In response, it is acknowledged that Green et al. was published after the priority date of the instant application. However, Green et al. teaches that the even after the time of filing, there were still issues regarding general/non-direct administration of oncolytic adenoviral vectors, which is indicative that the issues were also present at the time of filing.

Applicants submit that the reference of Green, et al., overall supports enablement of the present invention in regard to the use of multiple routes of delivery of adenoviral vectors beyond the scope limitation suggested by the Examiner in the rejection.

In response, Applicant is respectfully reminded that that MPEP § 2164.01 indicates that the application, at the time of filing, must contain sufficient information to enable one of skill in

the art how to make and use the claimed invention. Therefore, post-filing guidance which was not present in the application at the time of filing cannot be relied upon for establishing enablement at the time of filing. In the instant case, in view of the art of record which demonstrates that delivering a vector to specific target cells by general, non direct-delivery is unpredictable, the specification which only provides guidance for direct delivery, the specification does not provide an disclosure which enables the full scope encompassed by the claims.

Applicants also refer to a number of issued patents having claims drawn to methods of treatment using adenoviral vectors where the vectors are not limited to direct administration in the method of treatment.

In response, Applicants are respectfully reminded that every case is decided on its own merits. See *In re Giolito*, 530 F.2d 397, 400, 188 USPQ 645, 648 (CCPA 1976) which states:

> "We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others."

That other patents have been issued, based on different facts, is not evidence that the examiner's decision in this case, on these facts, is in error.

Therefore, Applicants arguments have been fully considered but are not persuasive and the instant claims stand rejected under 35 USC 112, first paragraph as the specification does not provide a disclosure which teaches on of skill in the art how to make and use the claimed invention to its full scope.

Allowable Subject Matter

Claims 26-28 are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on 9:00 a.m.- 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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